

REMARKS

Upon entry of the foregoing amendment, claims 1, 44-52, and 55-65 are pending in the application, with 1, 57-59, 61, and 63-65 being the independent claims. Claims 57-59, 61, and 63-65 have been amended to claim the invention with more particularity.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections Under 35 U.S.C. § 103

(A) Claims 1, 44–51, 55, and 56 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Teng *et al.* (WO 99/01579). (Office Action, page 3). Applicants respectfully traverse this rejection.

The Examiner alleges that Teng *et al.* teaches a composition and method for enhancing the transport of a nucleic acid drug in an animal and that the composition comprises various fatty acids and other penetration enhancers. (Office Action, page 3). The Examiner further alleges that Teng *et al.* teaches that the penetration enhancer can be caprylic acid or a sodium salt thereof and that the method can be used for transport of nucleic acids across and/or into cells of the alimentary canal. (Office Action, page 3). The Examiner further alleges that Teng *et al.* teaches that the enhancer can be caproate (C10) at a concentration of 1% (about 58 mM) and that the molar ratio of the enhancer and the nucleic acid is within the claimed range. (Office Action, page 4). The Examiner is of the opinion that oral administration of the composition taught by Teng *et al.* would necessarily result in contacting epithelial cells of the small intestine which would be effective for facilitating the intracellular delivery of the nucleic acid and must necessarily result in the intracellular delivery into the cytoplasm and/or nucleus of a cell resulting in homogenous distribution of the nucleic acid based compound in the cytoplasm and/or nucleus. (Office Action, pages 3-4). The Examiner acknowledges that Teng *et al.* does not teach that the C10 enhancer can be used at a concentration of about 0.013 mM to 13 mM, but alleges that it would have been *prima facie* obvious to perform routine experimentation to determine the optimum and/or workable ranges of concentrations for the C10 enhancer with a reasonable expectation of

success. (Office Action, page 4). The Examiner is further of the opinion that routine optimization is not considered inventive and no evidence has been presented that the selection of the specific concentration range was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. (Office Action, pages 4-5).

Applicants respectfully disagree. The Supreme Court has articulated that obviousness under § 103(a) is determined by an analysis of the following factors: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The obviousness or nonobviousness of the subject matter is to be determined based on these considerations however, secondary considerations such as commercial success, long-felt but unresolved needs and the failure of others can be utilized to determine the circumstances surrounding the origin of the invention. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1730 (2007). If such secondary considerations exist, they must be considered. See *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-1539 (Fed. Cir. 1983).

In *KSR*, the Supreme Court also made clear that predictable variations are likely obvious, but unpredictable variations are not:

If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative - a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

KSR at 1740.

The Court also recognized that when the prior art taught away from the claimed invention, the invention was more likely to be non-obvious: "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1996)).

The Court also emphasized the importance of identifying "a reason" that a person of ordinary skill in the relevant field would have combined the elements in the fashion claimed by the new invention. *Id.* at 1731. The Court also emphasized that this analysis should be made explicit:

Often it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

Id. at 1740-1741 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

The present invention is directed to a method for enhancing the intracellular delivery of a nucleic acid-based drug in a mammal comprising administering to the mammal, in combination with the nucleic acid-based drug, an enhancer in an amount effective to enhance the intracellular delivery of the nucleic acid-based drug, wherein the enhancer consists of a fatty acid or an ether, salt or anionic derivative thereof, wherein the fatty acid has a carbon chain length of 8 or 10 carbon atoms; the intracellular delivery is delivery into the cytoplasm and/or nucleus of a cell resulting in homogenous distribution of the nucleic acid-based compound in the cytoplasm and/or nucleus; and the intracellular delivery is facilitated by contacting the cell with an effective concentration of the enhancer; and wherein the amount of enhancer effective to enhance the intracellular delivery is about 0.013 mM to 13 mM when the enhancer has a carbon chain length of 10 carbon atoms and 0.12 mM to 120 mM when the enhancer has a carbon chain length of 8 carbon atoms.

Teng *et al.* is directed to compositions and methods for enhancing the transport of nucleic acids, such as oligonucleotides, across the mucosa of the alimentary canal of an animal through the use of one or more penetration enhancers (page 1, lines 9-12). The recited penetration enhancers enhance the stability of the nucleic acids and/or their transport across and/or into cells of the alimentary canal (page 1, lines 12-18). Teng *et al.* notes that certain penetration enhancers have been used to improve the bioavailability of certain drugs, but acknowledges that it is generally viewed to be the case that effectiveness of such penetration

enhancers is unpredictable (page 6, lines 17-22). Teng *et al.* describe five different classes of penetration enhancers: surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (page 9, lines 32-36). For fatty acids, Teng *et al.* indicate that capric acid (C10) and caprylic acid (C8) and their physiologically acceptable salts are included as possible enhancers (page 10, lines 17-31).

Notably, the general description of Teng *et al.* fails to mention a single word regarding the amount of penetration enhancer to include in compositions for delivering nucleic acids. Thus, any guidance to be derived from Teng *et al.* must be obtained from the examples. It is first pointed out that there are no examples of formulations comprising a C8 fatty acid. Thus, Teng *et al.* provides no guidance at all regarding effective ranges of C8 fatty acids. Example 3 (page 45) discloses formulations comprising an oligonucleotide and either 1% caprate (Formulation No. 1), 1% laurate (C12) (Formulation No. 2), or 0.5% laurate + 0.5% caprate (Formulation No. 3). 1% caprate is equivalent to a concentration of 51.5 mM, 1% laurate is equivalent to 44.8 mM, and 0.5% laurate + 0.5% caprate is equivalent to 48.2 mM. Example 4 (page 47) discloses the testing of these formulations in a rat ileum perfusion study. The results showed that there was no absorption of the oligonucleotide in the absence of an enhancer, that 1% caprate or 1% laurate resulted in 5% of the oligonucleotide being absorbed, and that the combination of caprate and laurate resulted in 15% absorption (page 48). The combination of Formulation No. 3 also produced blood levels of oligonucleotide that were 10-fold higher than with Formulation No. 1 (page 48). The tested concentrations of fatty acid in the range of 45-50 mM are well above the claimed range for C10 fatty acid of 0.13 to 13 mM in the present claims.

Example 7 (page 53) discloses formulations comprising both fatty acid enhancers and bile salt enhancers. The formulations and enhancer concentrations are shown in Table 1.

Table 1

	Formulation 15	Formulation 16	Formulation 17
Components	2% chenodeoxycholic acid (CDCA) + 0.5% caprate + 0.5% laurate	0.5% CDCA + 1% caprate + 1% laurate	1% CDCA + 1% ursodeoxycholic acid (UDCA) + 0.5% caprate + 0.5% laurate
Concentration fatty acids (mM)	48.2	96.5	48.2
Concentration bile acids (mM)	50.9	12.7	50.9
Concentration all enhancers (mM)	99.1	109.2	99.1
Absorption (%)	30.6	19.7	23.0
Blood concentration (%)	14.32	35.83	15.4

The results showed that higher concentrations of fatty acids produced higher oligonucleotide absorption rates compared to the lower fatty acid concentrations tested in Example 4. The results also show that the presence of additional penetration enhancers in the form of bile acids helped to increase the absorption rate. Importantly, the formulation having the highest concentration of fatty acids (96.5 mM) also produced the highest blood concentration of oligonucleotide, indicating that higher concentrations of fatty acids enhance delivery of oligonucleotides to the circulation.

Example 10 (page 57) tested formulations comprising even higher concentrations of fatty acids in a rat intrajejunal instillation assay. The formulations and enhancer

concentrations are shown in Table 2.

Table 2

	Formulation 18	Formulation 19	Formulation 20
Components	2% CDCA + 4% caprate + 4% laurate	2% UDCA + 4% caprate + 4% laurate	Microemulsion (Tween 80, Captex 355, Capmul MCM)
Concentration fatty acids (mM)	385.8	385.8	0
Concentration bile acids (mM)	50.9	50.9	0
Concentration all enhancers (mM)	436.7	436.7	0
Bioavailability liver (%)	17.4	8.8	19.8
Bioavailability kidney (%)	17.8	23.0	29.1

The results show that high bioavailabilities were achieved with the high concentrations of permeation enhancers, with bioavailabilities nearly as high as achieved with the microemulsion formulation in some instances. The bioavailability numbers in Example 10 cannot be directly compared to the numbers in the previous examples because of the different assays used, but it is clear that Teng *et al.* were testing increasingly higher concentrations of fatty acids and achieving high bioavailability rates.

Example 11 (page 59) tested the effect of increasing concentrations of oligonucleotide in 2% CDCA, 4% laurate and 4% caprate (Formulation 18). The results showed that increasing concentrations of oligonucleotides led to proportional increases in bioavailability, as well as the preference of Teng *et al.* for Formulation 18 comprising high concentrations of

fatty acids as an effective formulation.

Example 12 (page 60) tested the effect of different oligonucleotide chemistries on bioavailability, again using 2% CDCA, 4% laurate and 4% caprate (Formulation 18). The results again showed higher bioavailability numbers using this formulation compared to no enhancer or bile salt alone.

Example 13 (page 63) tested oligonucleotide availability in dogs after intrajejunal administration. Similar to the rat studies, the combination of fatty acids and bile salts (2% CDCA, 4% laurate and 4% caprate (Formulation 18)) produced higher bioavailabilities than either bile salts or fatty acids alone.

Example 14 (page 65) tested the effect of increasing concentrations of oligonucleotide in 2% CDCA, 4% laurate and 4% caprate (Formulation 18) on bioavailability in the dog intrajejunal administration model. The results showed that increasing concentrations of oligonucleotides led to decreases in bioavailability. Teng *et al.* concluded that as the proportion of penetration enhancers was decreased the bioavailability decreased, indicating that higher ratios of penetration enhancers to oligonucleotide are preferred.

Taken as a whole, the examples presented in Teng *et al.* would direct one of ordinary skill in the art to prepare formulations comprising high concentrations of fatty acids and preferably also including bile acids in order to optimize bioavailability. The experimental results clearly show that increasing the concentration of fatty acids up to about 386 mM provided improved bioavailability compared to lower concentrations. The experimental results also clearly show that the effect of these high concentrations of fatty acids were further improved by the inclusion of bile acids (*i.e.*, even more enhancer) in the formulation.

In contrast, the present claims are directed in part to methods using formulations comprising about 0.013 to 13 mM C10 fatty acid. The claimed range is about 4 to 4000-fold lower than the lowest concentration of fatty acid exemplified in Teng *et al.* (51.5 mM) and about 30 to 30,000-fold lower than the highest and preferred concentration of fatty acid exemplified in Teng *et al.* (385.8 mM). There is no evidence or suggestion in Teng *et al.* that the low levels of C10 fatty acid recited in the present claims would be effective to enhance intracellular delivery of a nucleic acid resulting in homogenous distribution of the nucleic acid in the cytoplasm and/or nucleus as is required by the claims. Thus, there is no incentive

for one to modify the teachings of Teng *et al.* to lower the concentration of C10 fatty acid in the formulations. Similarly, as Teng *et al.* is silent regarding concentrations of C8 fatty acids, there is no incentive provided by Teng *et al.* to try the particular concentrations recited in the present claims. In the absence of any direction or incentive, one would not have had a reasonable expectation that significantly lower concentrations of fatty acids could achieve the claimed activities. Furthermore, Teng *et al.* acknowledge the unpredictability of penetration enhancers for delivering nucleic acids (page 6, lines 17-22), emphasizing the lack of a reasonable expectation of success for the presently claimed low concentrations in light of the teachings of Teng *et al.*

In addition to failing to provide any incentive for modification, Teng *et al.* actually teaches away from lowering the concentration of enhancer below that disclosed in the examples. First, the series of examples disclosed in Teng *et al.* showed the trend that increasing concentrations of fatty acids led to higher bioavailability numbers. Further, the addition of a second class of enhancer (bile salts), thereby increasing the amount and proportion of enhancer in the formulation, improved bioavailability even further. Second, Teng *et al.* explicitly states that higher ratios of penetration enhancer to oligonucleotide are preferred to increase bioavailability (page 65, lines 21-27). In view of these teachings, Teng *et al.* clearly teaches away from lowering the concentration of fatty acid enhancer in the formulation and thereby lowering the ratio of penetration enhancer to oligonucleotide. Obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). Here, Teng *et al.* clearly teaches that higher amounts of fatty acids and a high ratio of penetration enhancer to oligonucleotide improve bioavailability, thereby directly teaching away from significantly lowering the fatty acid concentration. Thus, the present claims cannot be obvious over Teng *et al.*

It is respectfully requested that the rejection of claims 1, 44–51, 55, and 56 under 35 U.S.C. § 103(a) be withdrawn.

(B) Claims 1 and 52 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Teng *et al.* in view of Lewin *et al.* (GB 23197673). (Office Action, page 5). Applicants respectfully traverse this rejection.

The Examiner alleges that Teng *et al.* is applied as above but does not teach that the nucleic acid based drug is a gene coding for an RNA molecule which functions in an antisense capacity. (Office Action, page 5). The Examiner alleges that Lewin *et al.* teaches a nucleic acid vector which comprises a gene that expresses an RNA molecule which functions as an antisense oligonucleotide in a cell. (Office Action, page 5). The Examiner is of the opinion that it would have been *prima facie* obvious to modify the composition and method taught by Teng *et al.* to use the vector taught by Lewin *et al.* with a reasonable expectation of success, motivated by the knowledge of one of ordinary skill in the art that the vector could be used to produce large amounts of antisense RNA (Office Action, pages 5-6).

Applicants respectfully disagree. As described above, Teng *et al.* fails to teach or provide any incentive to use the concentration of enhancer as set forth in the present claims and in fact teaches away from the low concentrations claimed. Lewin *et al.* fails to make up for the deficiencies of Teng *et al.* Lewin *et al.* describes a vector for expression of antisense RNA in cells (see Table 1). However, Lewin *et al.* is silent regarding the use of fatty acid enhancers. Lewin *et al.* does not provide any incentive to modify the teachings of Teng *et al.* by lowering the concentration of enhancer. Thus, the present claims cannot be obvious over the cited combination of references.

It is respectfully requested that the rejection of claims 1 and 52 under 35 U.S.C. § 103(a) be withdrawn.

(C) Claims 57, 58, and 63-65 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Teng *et al.* in view of Akhtar (J. Drug Targeting 5:225 (1998)). (Office Action, page 6). Applicants respectfully traverse this rejection.

The Examiner alleges that Teng *et al.* is applied as above but does not teach that (1) the oligonucleotide is complexed with a cationic lipid or a polymer system; (2) an endosomal escape/nuclear accumulation agent can be used to facilitate delivery; (3) a condensing agent can be used to condense the oligonucleotide and facilitate delivery; and (4) a condensing

agent can be used to condense the oligonucleotide and the oligonucleotide is complexed with a cationic lipid to facilitate delivery. (Office Action, page 7). The Examiner alleges that Akhtar teaches a number of different means for facilitating delivery of antisense oligonucleotides into cells including the use of cationic lipids, polymer microspheres and agents to improve endosomal exit. (Office Action, page 7). The Examiner is of the opinion that it would have been *prima facie* obvious that delivery of the antisense oligonucleotide composition of Teng *et al.* could be facilitated using the means described in Akhtar with a reasonable expectation of success, motivated by the teaching of Akhtar that the means for facilitating delivery improves cellular delivery of antisense oligonucleotides. (Office Action, page 7).

Applicants respectfully disagree. As described above, Teng *et al.* fails to teach or provide any incentive to use the concentration of enhancer as set forth in the present claims and in fact teaches away from the low concentrations claimed. Akhtar fails to make up for the deficiencies of Teng *et al.* Akhtar discusses the delivery of antisense oligonucleotides and mentions the use of different means for facilitating delivery (see Table 1). However, Akhtar is silent regarding the use of fatty acid enhancers. Akhtar does not provide any incentive to modify the teachings of Teng *et al.* by lowering the concentration of enhancer. Thus, the present claims cannot be obvious over the cited combination of references.

It is respectfully requested that the rejection of claims 57, 58, and 63-65 under 35 U.S.C. § 103(a) be withdrawn.

(D) Claims 58-60 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Teng *et al.* in view of Akhtar (*J. Drug Targeting* 5:225 (1998)) and Akhtar *et al.* (*Int. J. Pharmaceutics* 151:57 (1997)). (Office Action, page 7). Applicants respectfully traverse this rejection.

The Examiner alleges that Teng *et al.* is applied as above but does not teach that (1) the oligonucleotide is complexed with a cationic lipid or a polymer system; (2) an endosomal escape/nuclear accumulation agent can be used to facilitate delivery; (3) a condensing agent can be used to condense the oligonucleotide and facilitate delivery; and (4) a condensing agent can be used to condense the oligonucleotide and the oligonucleotide is complexed with

a cationic lipid to facilitate delivery. (Office Action, page 8). The Examiner alleges that Akhtar teaches a number of different means for facilitating delivery of antisense oligonucleotides into cells including the use of polymer microspheres and that Akhtar *et al.* teaches that biodegradable polymers can be used to facilitate delivery of antisense oligonucleotides into cells, wherein the antisense oligonucleotide is complexed with (entrapped in) the polymer. (Office Action, page 9). The Examiner is of the opinion that it would have been *prima facie* obvious that the antisense oligonucleotide composition of Teng *et al.* could be complexed with (entrapped in) a biodegradable polymer (such as PLGA) as taught by Akhtar *et al.* to facilitate the delivery of the oligonucleotide composition with a reasonable expectation of success, motivated by the teaching of Akhtar *et al.* that PLGA improves cellular delivery of antisense oligonucleotides. (Office Action, page 9).

Applicants respectfully disagree. As described above, Teng *et al.* fails to teach or provide any incentive to use the concentration of enhancer as set forth in the present claims and in fact teaches away from the low concentrations claimed. Akhtar and Akhtar *et al.* both fail to make up for the deficiencies of Teng *et al.* Akhtar discusses the delivery of antisense oligonucleotides and mentions the use of polymer matrices (see page 231 and Table 1). However, Akhtar is silent regarding the use of fatty acid enhancers. Akhtar *et al.* discusses delivery of antisense oligonucleotides to cultured macrophages using biodegradable polymer (P(LA-GA)) particles (see abstract). However, Akhtar *et al.* is silent regarding the use of fatty acid enhancers. Neither reference provides any incentive to modify the teachings of Teng *et al.* by lowering the concentration of enhancer. Thus, the present claims cannot be obvious over the cited combination of references.

It is respectfully requested that the rejection of claims 58-60 under 35 U.S.C. § 103(a) be withdrawn.

(E) Claims 61 and 62 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Teng *et al.* in view of Nakashima (J. Pharm. Sci. 84:1205 (1995)). (Office Action, page 9). Applicants respectfully traverse this rejection.

The Examiner alleges that Teng *et al.* is applied as above but does not teach that a P-glycoprotein inhibitor is administered with the antisense oligonucleotide composition.

(Office Action, pages 9-10). The Examiner alleges that Nakashima *et al.* teaches that verapamil, a P-glycoprotein inhibitor, can be used in low doses in combination with antisense oligonucleotides to increase the efficacy of the antisense oligonucleotide treatment (Office Action, page 10). The Examiner is of the opinion that it would have been *prima facie* obvious to use verapamil in combination with antisense oligonucleotide compositions taught by Teng *et al.* with a reasonable expectation of success, motivated by the teaching of Nakashima *et al.* that low doses of the inhibitor increases the efficacy of the antisense oligonucleotide. (Office Action, pages 10-11).

Applicants respectfully disagree. As described above, Teng *et al.* fails to teach or provide any incentive to use the concentration of enhancer as set forth in the present claims and in fact teaches away from the low concentrations claimed. Nakashima *et al.* fails to make up for the deficiencies of Teng *et al.* Nakashima *et al.* discloses the use of an antisense oligonucleotide to the mdr1 mRNA (encoding P-glycoprotein) to reverse multidrug resistance in leukemia cell lines (abstract). Nakashima teaches that the addition of verapamil increased the reversal of resistance by the antisense oligonucleotide (page 1208, column 1, first full paragraph), due to verapamil's action as a strong inhibitor of P-glycoprotein (page 1206, column 2, last paragraph). Thus, verapamil is not associated in any way with enhanced delivery of the antisense oligonucleotide. Nakashima *et al.* is silent regarding the use of fatty acid enhancers. Thus, the present claims cannot be obvious over the cited combination of references.

It is respectfully requested that the rejection of claims 61 and 62 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants believe that the points and concerns raised by the Examiner in the Action have been addressed in full. It is respectfully submitted that this application is in condition for allowance, which action is earnestly solicited. Should the Examiner have any remaining concerns, it is respectfully requested that the Examiner contact the undersigned Attorney at (919) 854-1400 to expedite the prosecution of this application to allowance.

No fee is believed to be due with this response. However, the Commissioner is

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hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

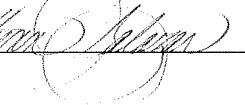


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